Interdisciplinary Complex Systems: Theoretical Physics Methods in Systems Biology.

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0.1 Topics

- Reaction-diffusion equations
- Turbulence in vortex dynamics
- Heat Transfer in excitable tissues
- Mechano-electric Feedback
- Computational Cardiology
- Mathematical Models of Tumor Growth

0.2 Participants

0.2.1 ICRANet participants

- Donato Bini (IAC, CNR, Rome, Italy)
- Christian Cherubini (University Campus Bio-Medico, Rome, Italy)
- Simonetta Filippi, project leader (University Campus Bio-Medico, Rome, Italy)

0.3 External Collaborations

- Valentin Krinsky(INLN,CNRS, Nice, France)
- Alain Pumir(INLN,CNRS, Nice, France)
- Flavio Fenton and Elizabeth Cherry (Biosciences Department, Cornell University, USA)

0.3.1 Students

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0.4 Brief description

This group has started recently the study of problems of nonlinear dynamics of complex systems focusing on biological problems using a theoretical physics approach. The term "biophysics" is today changing in its meaning and appears not to be sufficient to contain areas like "theoretical biology", "living matter physics" of "complex biological systems". On the other hand, the term "Theoretical Physics applied to biological systems" appears to be wide enough to describe very different areas. It is well established both numerically and experimentally that nonlinear systems involving diffusion, chemotaxis, and/or convection mechanisms can generate complicated time-dependent patterns. Specific examples include the Belousov-Zhabotinskii reaction ,the oxidation of carbon monoxide on platinum surfaces, slime mold, the cardiac muscle, nerve fibres and more in general excitable media. Because this phenomenon is global in nature, obtaining a quantitative mathematical characterization that to some extent records or preserves the geometric structures of the complex patterns is difficult.

Following Landau's course in theoretical physics, we have worked in Theoretical Biophysics focusing our studies on pathological physiology of cardiac and neural tissues. Finite element simulations of electro-thermo-visco-elastic models describing heart and neural tissue dynamics in 1D and 2D have been performed ([1],[2]), finding a possible experimental way to evidence the topological defects which drive the spiral associated with typical arrythmias (Figure 1), typical of reaction diffusion equations, whose prototype, with two variables for the sake of simplicity, is shown below

$$\begin{aligned} V_t &= D_1 \nabla^2 V + f(U,V) \\ U_t &= D_2 \nabla^2 U + g(U,V)\,, \end{aligned} \tag{0.1}$$

where the V variable refers to an activator and the U variable to the inhibitor respectively. The f and g terms are typically highly nonlinear in U and V. We have analyzed [3] in particular the coupling of the reaction-diffusion equations governing the electric dynamics of the tissue with finite elasticity (see Figures 2, 3 and 4). The problem, due to the free boundary conditions, must be formulated in weak form (integral form) of deformable domains, and requires massive use of differential geometry and numerical techniques like finite elements methods. The experience obtained in this field will be adapted in future studies for problems of self-gravitating systems and cosmology. Moreover computational cardiology and neurology for cancer research in 3D using NMR imported real heart geometries have been studied ([4]-[6]) (Figures 5,6 and 7). More in detail the RMN import of a real brain geometry in Comsol Multiphysics (a powerful finite element PDEs solver) via an interpolating function has been performed. The physical property associated with the greyscale is the diffusivity tensor, assumed to be isotropic but inhomogeneous. Applications to antitumoral drug delivery and cancer growth processes have been presented. In 2009 specifically the group has published an article on heat transfer in excitable biological tissues of neural type extending the previous studies focused on the FitzHugh-Nagumo model. More in detail, an extension of the Hodgkin-Huxley mathematical model for the propagation of nerve signal taking into account dynamical heat transfer in biological tissue has been derived in accordance with existing experimental data[7]. The model equations, summarized are:

$$\begin{aligned} C_m \frac{\partial V}{\partial t} &= \vec{\nabla} \cdot (\hat{G}\vec{\nabla} V) + \eta(T)[g_{Na} m^3 h (V_{Na} - V) + g_K n^4 (V_K - V) + g_\ell (V_\ell - V)]\,, \\ \frac{\partial m}{\partial t} &= \phi(T)[\alpha_m(V)(1-m) - \beta_m(V) m]\,, \\ \frac{\partial h}{\partial t} &= \phi(T)[\alpha_h(V)(1-h) - \beta_h(V) h]\,, \\ \frac{\partial n}{\partial t} &= \phi(T)[\alpha_n(V)(1-n) - \beta_n(V) n]\,. \end{aligned} \tag{0.2}$$

where $\alpha_j(V), \beta_j(V)$ (with $j = m, n, h$) are specific functions (the rate constants) of the form

$$\begin{aligned} \alpha_n(V) &= \frac{0.01(10+V)}{[e^{(10+V)/10} - 1]}\,, \quad \beta_n(V) = 0.125 e^{V/80}\,, \\ \alpha_m(V) &= \frac{0.1(25+V)}{[e^{(25+V)/10} - 1]}\,, \quad \beta_m(V) = 4 e^{V/18}\,, \\ \alpha_h(V) &= 0.07 e^{V/20}\,, \qquad \beta_h(V) = \frac{1}{e^{(30+V)/10} + 1}\,, \end{aligned} \tag{0.3}$$

$$\underbrace{\rho\, c_p\, \partial_t T}_{\text{energy storage rate}} = \underbrace{\nabla_i (k_{il} \nabla_\ell T)}_{\text{conduction}} + \underbrace{\sigma_{ik} \nabla_i V \nabla_k V}_{\text{heat source}} + \underbrace{w_*(T_* - T)}_{\text{perfusion-sink}}\,, \tag{0.4}$$

(the meaning of the remaining quantities can be found in the publication relative to this study). The medium, heated by the Joule's effect associated with action potential propagation, manifests characteristic thermal patterns (see figure0.8 and 0.9) in association with spiral and scroll waves. The introduction of heat transfer—necessary on physical grounds—has provided a novel way to directly observe the movement, regular or chaotic, of the tip of 3D scroll waves in numerical simulations and possibly in experiments. The model will open new perspective also in the context of cardiac dynamics: at the moment in fact the authors are approaching the problem in the same context. The group has also developed a more fundamental study on general theory of reaction diffusion [8]. It is commonly accepted in fact that reaction-diffusion equations cannot be obtained by a Lagrangian formulation. Guided by the well known connection between quantum and diffusion equations, we implemented a Lagrangian approach valid for totally general nonlinear reacting-diffusing systems allowing the definition of global conserved observables derived using Noethers theorem. Specifically, for the case of two diffusing species, denoting with an odd suffix the physical real field and with an even one the auxiliary ones, we define the following Lagrangian density

$$\begin{aligned}\mathcal{L} = & - D_1(\nabla\psi_2)\cdot(\nabla\psi_1) - D_2(\nabla\psi_4)\cdot(\nabla\psi_3) + \\ & - \frac{1}{2}\left(\psi_2\frac{\partial\psi_1}{\partial t} - \psi_1\frac{\partial\psi_2}{\partial t}\right) + S(\psi_1,\psi_3)(\psi_2 - C_1) + \\ & - \frac{1}{2}\left(\psi_4\frac{\partial\psi_3}{\partial t} - \psi_3\frac{\partial\psi_4}{\partial t}\right) + H(\psi_1,\psi_3)(\psi_4 - C_2)\,.\end{aligned} \tag{0.5}$$

This quantity, once inserted into Euler-Lagrange equations gives:

$$\begin{aligned}\frac{\partial\psi_2}{\partial t} &= -D_1\nabla^2\psi_2 + \frac{\partial S}{\partial\psi_1}(C_1-\psi_2) + \frac{\partial H}{\partial\psi_1}(C_2-\psi_4)\\ \frac{\partial\psi_4}{\partial t} &= -D_2\nabla^2\psi_4 + \frac{\partial S}{\partial\psi_3}(C_1-\psi_2) + \frac{\partial H}{\partial\psi_3}(C_2-\psi_4)\\ \frac{\partial\psi_1}{\partial t} &= D_1\nabla^2\psi_1 + S(\psi_1,\psi_3)\\ \frac{\partial\psi_3}{\partial t} &= D_2\nabla^2\psi_3 + H(\psi_1,\psi_3)\,,\end{aligned} \tag{0.6}$$

Noether's theorem then can be adopted to obtain conserved quantities as summarized in figures 10-13 for FitzHugh-Nagumo model. In 2009 the group has published a chapter devoted on mathematical modelling of cardiac tissue dynamics on a monograph on Mechano-sensitivity in biological cells [9].

0.5 2010 results

In 2010 the group has published a series of works regarding the role of spiral structures in nature, more in detail in cardiology and in intestinal electrophysiology. Spiral waves as already discussed appear in many different natural contexts. It has been explored the fact that self-sustained spiral wave regime is already present in the linear heat operator, in terms of integer Bessel functions of complex argument, which although diverging at spatial infinity, play a central role in the understanding of the universality of spiral process. Nonlinearities in fact correct the divergences. Let's take the dimensionless diffusion equation

$$\frac{\partial C}{\partial T} = \nabla^2 C \tag{0.7}$$

where ∇^2 denotes here the Laplacian in dimensionless Cartesian coordinates. It is convenient to write the diffusion equation above in dimensionless cylindrical coordinates (R, ϕ, Z) with R and ϕ defined so that

$$(X, Y) = R(\cos\phi\,, \sin\phi)\,. \tag{0.8}$$

We use then the following separation of variables *ansatz*

$$C(R, \phi, Z, T) = P(R)e^{i\omega T + ikZ + im\phi}. \tag{0.9}$$

The linearity of the problem ensures us that the real and imaginary parts of this quantity both are solutions of Eq. (0.7). Solutions in cylindrical coordinates are

$$C = (\mathrm{Re}[J_m(\zeta)] + i\mathrm{Im}[J_m(\zeta)])e^{i\omega T + ikZ + im\phi} \equiv \mathrm{Re}[C] + i\,\mathrm{Im}[C] \tag{0.10}$$

where

$$\begin{aligned} \mathrm{Re}[C] &= \mathrm{Re}[J_m(\zeta)]\cos(\omega T + kZ + m\phi) - \mathrm{Im}[J_m(\zeta)]\sin(\omega T + kZ + m\phi) \\ \mathrm{Im}[C] &= \mathrm{Re}[J_m(\zeta)]\sin(\omega T + kZ + m\phi) - \mathrm{Im}[J_m(\zeta)]\cos(\omega T + kZ + m\phi)\ . \end{aligned} \tag{0.11}$$

When $k = 0$, i.e. an infinite cylinder solution, the real and imaginary parts of C give moving target patterns and rotating spirals of various chiralities and numbers of arms as shown at a fixed time in Fig. 0.14. We have then extended our discussion including nonlinearities typical of reaction-diffusion problems showing that these spirals diverging at infinity get bound instead by nonlinear terms.

The next topic of research has been a study of the pinning properties of reaction-diffusion induced vortices by impurtities/anatomical obstacles in cardiac tissue (see Fig. 0.15). What there has been found is that unpinning of vortices attached to obstacles smaller than the core radius of the free vortex is possible through pacing. The wave-train frequency necessary for unpinning increases with the obstacle size and we present a geometric explanation of this dependence. These results can have dramatic relevance for saving lives in dangerous cases of fibrillation.

We have finally concluded our studies by understanding the potential role of temperature gradients (typical of surgery theater) in producing turbulent behaviors in the underlying nonlinear electrophysiology of intestine. This study can have important applications in avoiding a common outcome of abdominal surgery, the postoperative paralytic ileus which increases the amount of time spent by the patient in hospital causing an increase of general costs. Schematic field equations (of reaction-diffusion class together with bio-heat diffusion equation), numerically integrated via finite element methods are, for the electrophysiology of the double layered intestinal domain (v and u are electrical variables)

$$\partial_t u_l = f\left(u_l\right) + D_l \nabla^2 u_l - v_l + F_l\left(u_l, u_i\right)$$

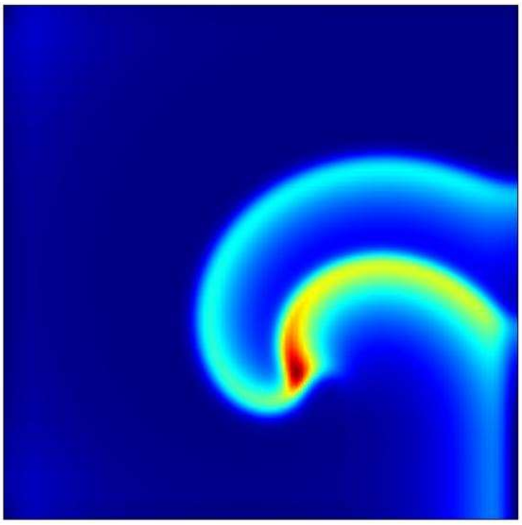

Figure 0.1: Spiral wave in the temperature domain at a given time.

$$\begin{aligned}
\partial_t v_l &= \varepsilon_l[\gamma_l (u_l - \beta_l) - v_l] \\
\partial_t u_i &= g(u_i) + D_i \nabla^2 u_i - v_i + F_i(u_l, u_i) \\
\partial_t v_i &= \varepsilon_i(z)[\gamma_i (u_i - \beta_i) - v_i], \qquad (0.12)
\end{aligned}$$

together with the thermal diffusion equation (T stands for temperature)

$$C\partial_t T - k\nabla^2 T - w_m(T) C_b (T_a - T) - q_m(T) - p(\mathbf{x}, t) = 0. \qquad (0.13)$$

In Fig 0.16 we show a typical electrical turbulent situation generated by temperature gradients on a model of an intestinal segment.

0.6 Publications (2005-2010)

1. Bini D., Cherubini C., Filippi S., "Heat Transfer in FitzHugh-Nagumo models," Physical Review E, Vol. 74 041905 (2006).

   Abstract: An extended FitzHugh-Nagumo model coupled with dynamic al heat transfer in tissue, as described by a bioheat equation, is derived and confronted with experiments. The main outcome of this analysis is that traveling pulses and spiral waves of electric activity produce temperature variations on the order of tens of C . In particular, the model predicts that a spiral wave's tip, heating the surrounding medium as a consequence of the Joule effect, leads to characteristic hot spots. This process could possibly be used to have a direct visualization of the tip's position by using thermal detectors

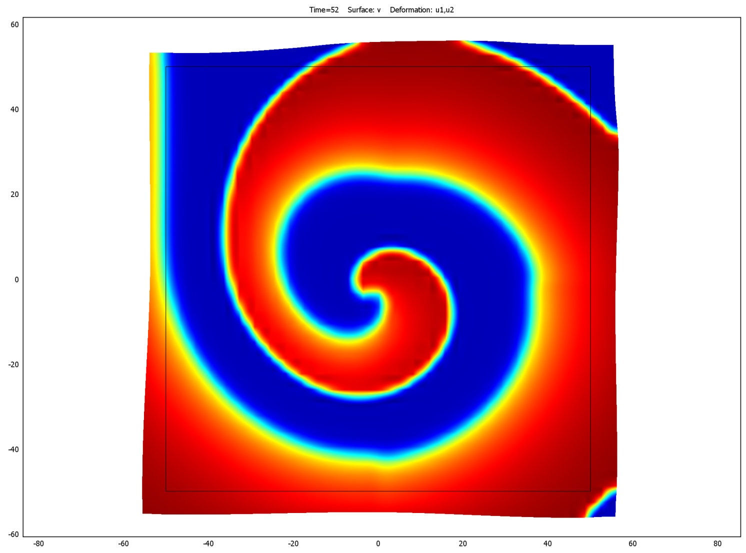

Figure 0.2: 2D Evolution of a spiral wave in voltage domain coupled to finite elastic deformations at a given time.

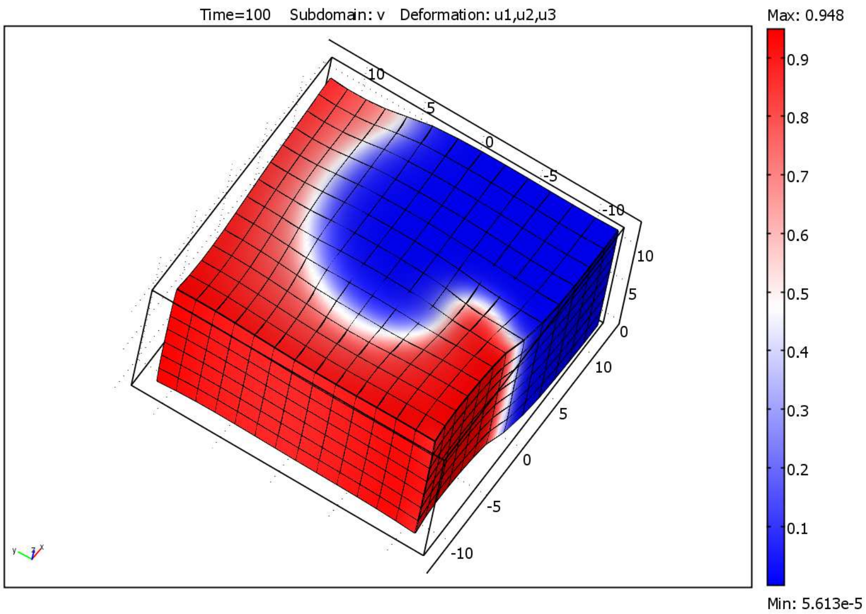

Figure 0.3: 3D spiral wave coupled to strong mechanical deformations.

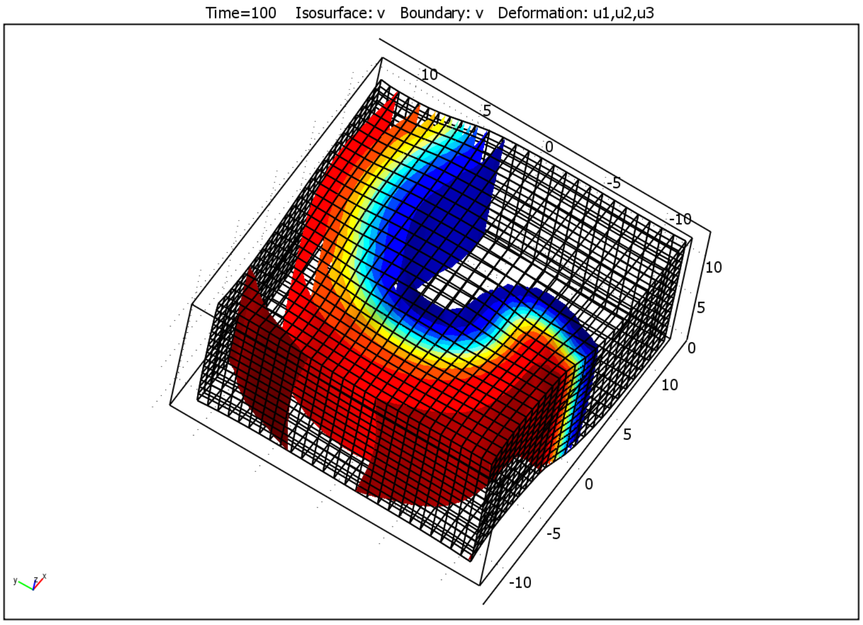

Figure 0.4: 3D spiral waves iso-voltage lines embedded in a mechanically deformed domain.

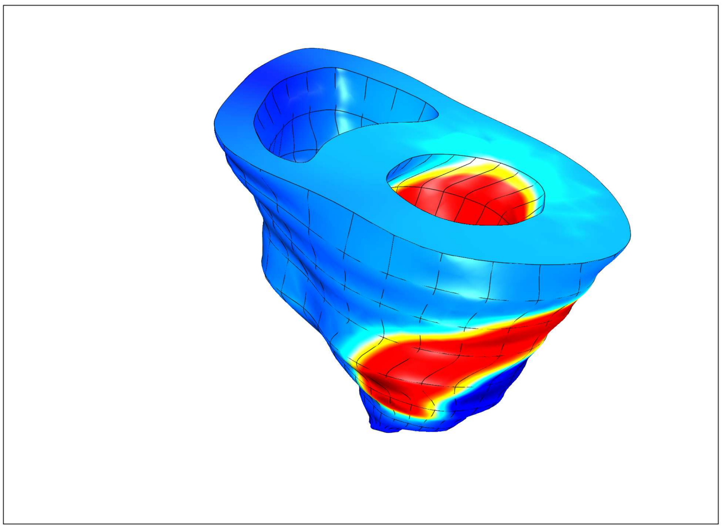

Figure 0.5: Voltage distribution at a given time on a real 3D NMR imported heart geometry.

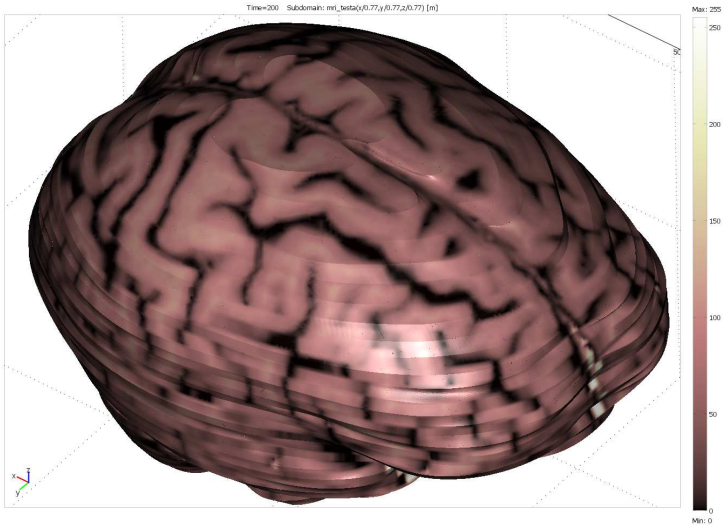

Figure 0.6: 3D NMR imported brain geometry associated with a diffusion tensor.

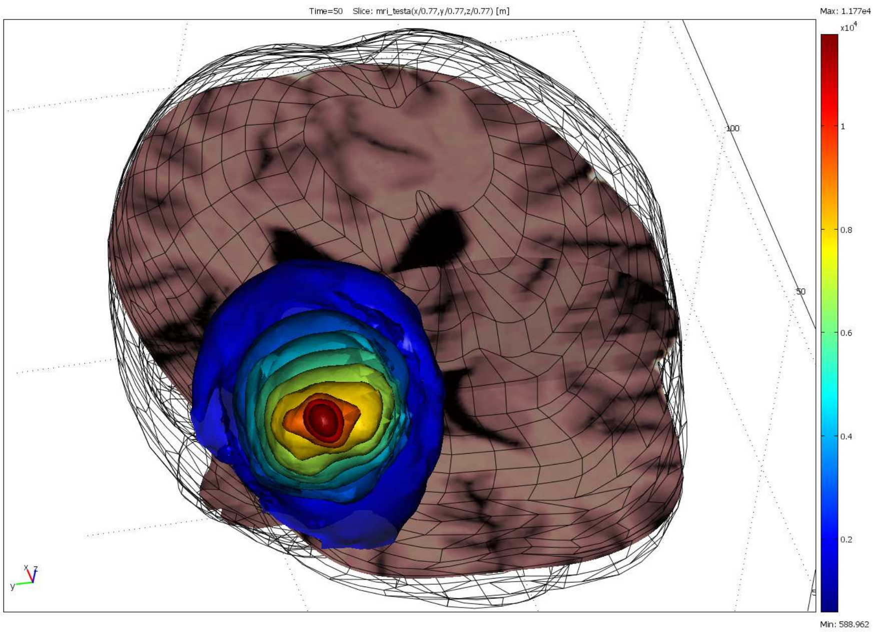

Figure 0.7: Mathematical model of tumor growth on the reconstructed brain geometry.

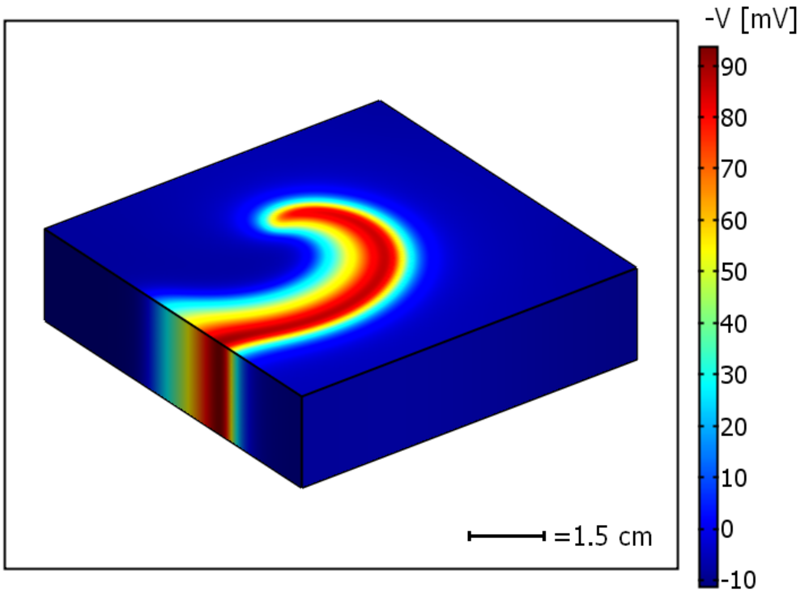

Figure 0.8: 3D scroll wave of action potential

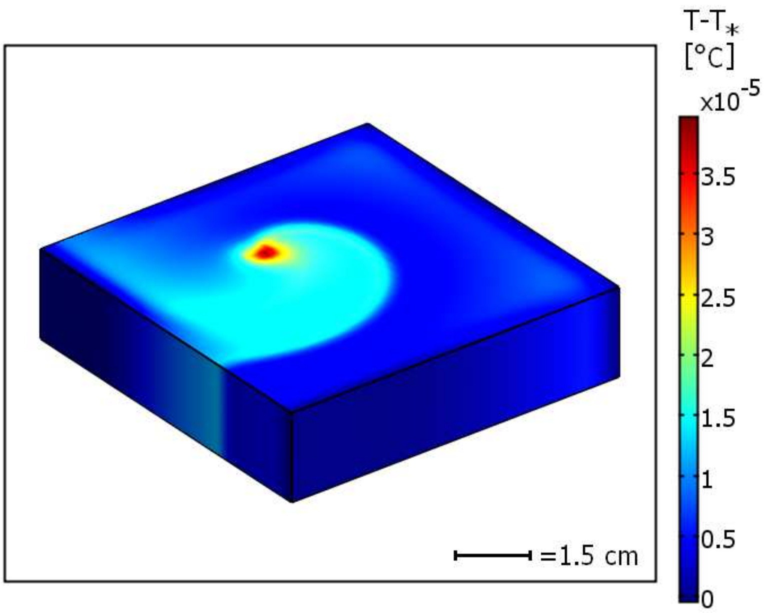

Figure 0.9: 3D thermal pattern associated with the electric scroll wave of the previous figure.

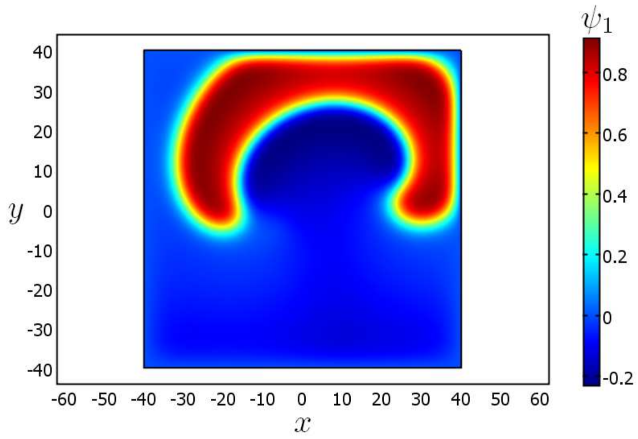

Figure 0.10: Case A: spiral waves of variable ψ_1: notice the Dirichlet boundary condition behavior of the spiral to be confronted with case B simulations.

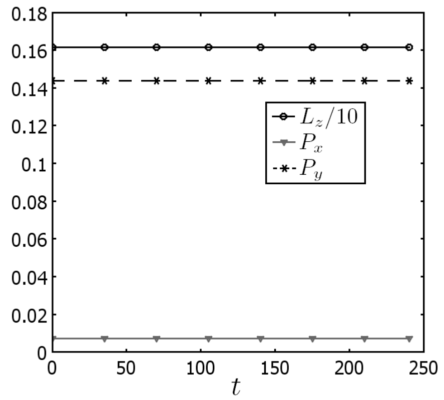

Figure 0.11: Case A: Total angular momentum L_z, and total field momenta P_x and P_y in time: conservation laws hold for all these quantities.

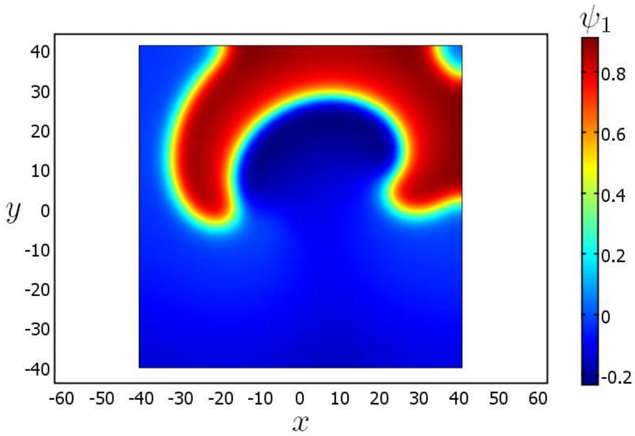

Figure 0.12: Case B: spiral waves of variable ψ_1: notice the typical Neumann zero flux boundary condition behavior of the spirals.

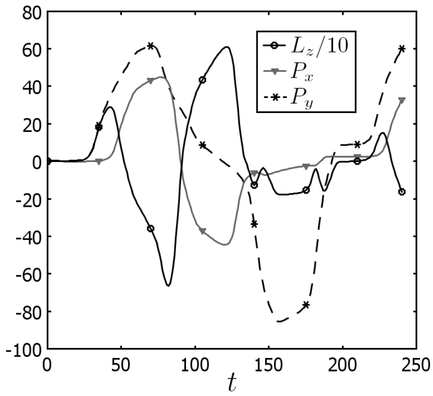

Figure 0.13: Case B: Total angular momentum L_z, and total field momenta P_x and P_y in time: conservation laws do not hold for all these quantities.

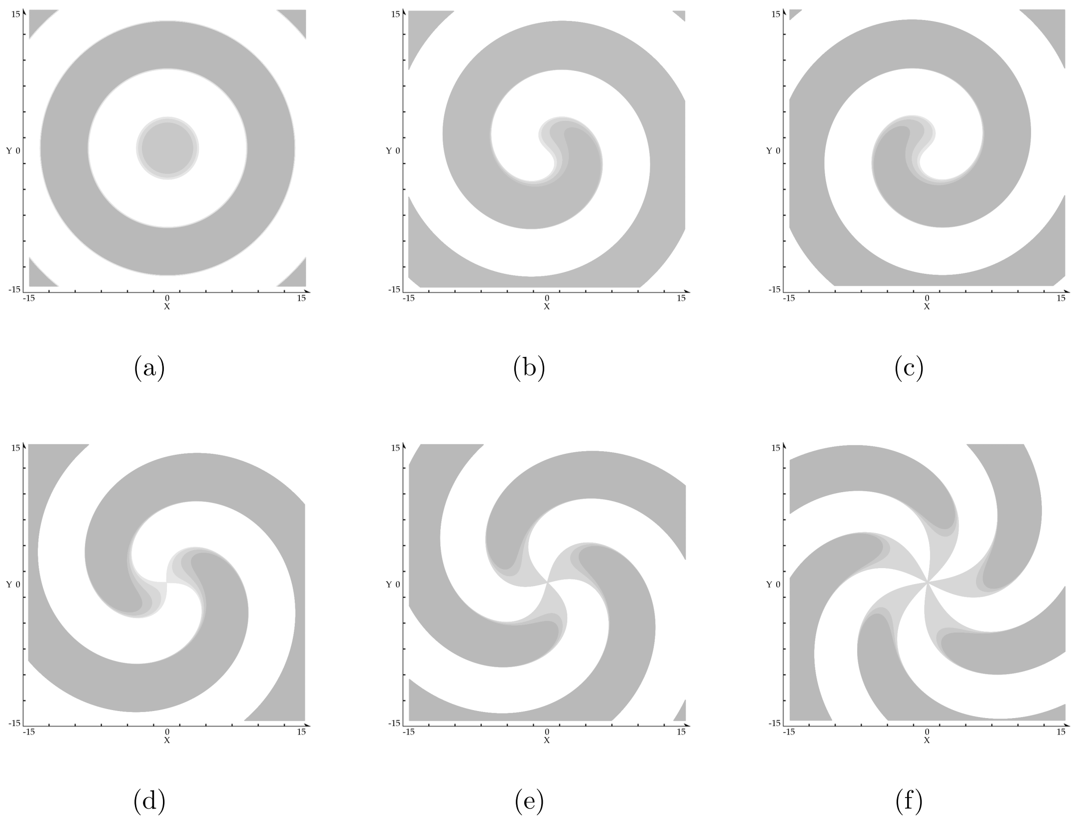

Figure 0.14: Real part of C (solution of the diffusion problem (0.7)), at $T = 0$ assuming moreover $k = 0$ (cylindrical symmetry). Surface levels $C = (0, 0.15, 0.5, 1)$ are shown (grey color means high values while white is the opposite). For different m one obtains the following patterns: a) for $m = 0$ which is reminiscent of target patterns b) $m = 1$ which is a spiral c) $m = -1$ is a spiral with opposite chirality d) $m = 2$ a two armed spiral e) $m = 3$ a three armed spiral f) $m = -5$ a five armed spiral with opposite chirality.

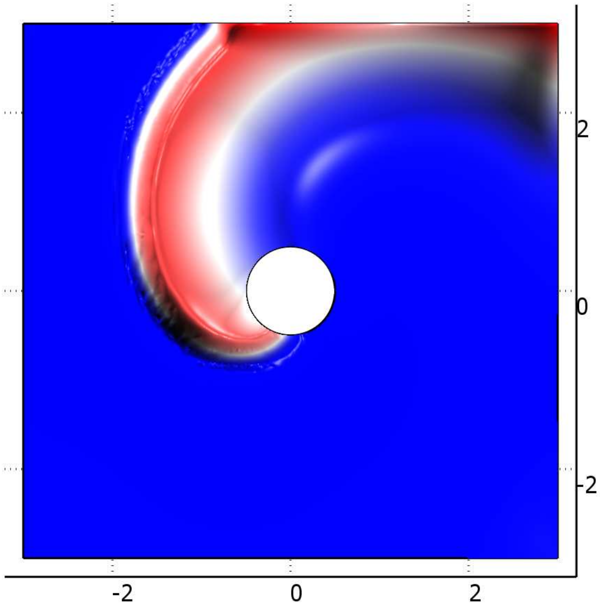

Figure 0.15: Action potential electrical configuration of a vortex pinned by a large spherical hole. The obstacle in this case acts as an attracting center for these arrhythmical configurations which must be mandatorily detached and pushed on the boundary in order to annihilate it.

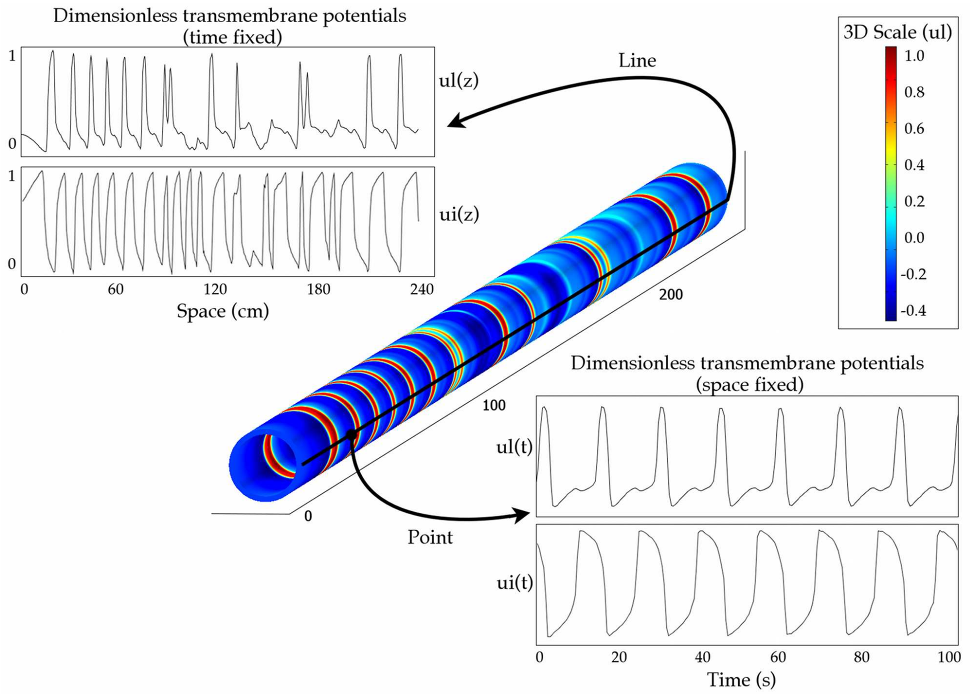

Figure 0.16: Schematic representation of the 3D FEM ionic intestine model. In figure the point-time evolution and the line-space distribution of the two transmembrane ionic potentials, u_l and u_i are described. These are both referred to the three-dimensional regime state of intestine activity simulated.

2. Bini D., Cherubini C., Filippi S., "Viscoelastic FitzHugh-Nagumo models," Physical Review E, Vol. 72 041929 (2005).

Abstract: An extended Fitzhugh-Nagumo model including linear viscoelastici ty is derived in general and studied in detail in the one-dimensional case. The equations of the theory are numerically integrated in two situations: i) a free insulated fiber activated by an initial Gaussian distribution of action potential, and ii) a clamped fiber stimulated by two counter phased currents, located at both ends of the space domain. The former case accounts for a description of the physiological experiments on biological samples in which a fiber contracts because of the spread of action potential, and then relaxes. The latter case, instead, is introduced to extend recent models discussing a strongly electrically stimulated fiber so that nodal structures associated on quasistanding waves are produced. Results are qualitatively in agreement with physiological behavior of cardiac fibers. Modifications induced on the action potential of a standard Fitzhugh-Nagumo model appear to be very small even when strong external electric stimulations are activated. On the other hand, elastic backreaction is evident in the model

3. Cherubini C., Filippi S., Nardinocchi P., Teresi L., "An electromechanical model of cardiac tissue: Constitutive issues and electrophysiological effects," Progress in Biophysics and Molecular Biology vol. 97, 562−573 (2008)

Abstract: We present an electromechanical model of myocardium tissue coupling a modified FitzHughNagumo type system, describing the electrical activity of the excitable media, with finite elasticity, endowed with the capability of describing muscle contractions. The high degree of deformability of the medium makes it mandatory to set the diffusion process in a moving domain, thereby producing a direct influence of the deformation on the electrical activity. Various mechanoelectric effects concerning the propagation of cylindrical waves, the rotating spiral waves, and the spiral breakups are discussed

4. S.Filippi, C.Cherubini, Electrical Signals in a Heart, Comsol Multiphysics Model Library, Sept. p.106-116.(2005)

5. S.Filippi, C.Cherubini, Models of Biological System, Procceedings of COMSOL Conference, Milan (2006).

Abstract: This article discusses the RMN import of a brain geometry in Comsol Multiphysics via an interpolating function. The physical property associated with the grayscale is the diffusivity tensor, assumed here to be isotropic but inhomogeneous. Applications to antitumoral drug delivery and cancer growth processes are discussed.

6. C.Cherubini, S.Filippi, A.Gizzi, Diffusion processes in Human Brain using Comsol Multiphysics, Procceedings of COMSOL Conference, Milan (2006).

Abstract:This article presents different applications of Comsol Multiphysics in the context of mathematical modeling of biological systems. Simulations of excitable media like cardiac and neural tissues are discussed.

7. Bini D., Cherubini C., Filippi S., "On vortices heating biological excitable media," Chaos, Solitons and Fractals vol. 42 (2009) 20572066

   Abstract: An extension of the HodgkinHuxley mathematical model for the propagation of nerve signal which takes into account dynamical heat transfer in biological tissue is derived and fine tuned with existing experimental data. The medium is heated by Joules effect associated with action potential propagation, leading to characteristic thermal patterns in association with spiral and scroll waves. The introduction of heat transfernecessary on physical groundsprovides a novel way to directly observe the movement, regular or chaotic, of the tip of spiral waves in numerical simulations and possibly in experiments regarding different biological excitable media.

8. Cherubini C. and Filippi S., "Lagrangian field theory of reaction-diffusion," Physical Review E, Vol. 80 046117 (2009).

   Abstract: It is commonly accepted that reaction-diffusion equations cannot be obtained by a Lagrangian field theory. Guided by the well known connection between quantum and diffusion equations, we implement here a Lagrangian approach valid for totally general nonlinear reacting-diffusing systems which allows the definition of global conserved observables derived using Nthers theorem

9. Cherubini C., Filippi S., Nardinocchi P., Teresi L., "Electromechanical modelling of cardiac tissue", in "Mechanosensitivity of the Heart Series: Mechanosensitivity in Cells and Tissues , Vol. 3", Kamkin, A.; Kiseleva, I. (Eds.) (2009), Springer.

10. D. Bini, C. Cherubini, S. Filippi, A.Gizzi and P. E. Ricci, "On Spiral Waves Arising in Natural Systems", Commun. Comput. Phys. Vol. 8, No. 3, pp. 610-622 (2010)

    Abstract: Spiral waves appear in many different natural contexts: excitable biological tissues, fungi and amoebae colonies, chemical reactions, growing crystals, fluids and gas eddies as well as in galaxies. While the existing theories explain the presence of spirals in terms of nonlinear parabolic equations, it is explored here the fact that self-sustained spiral wave regime is already present in the linear heat operator, in terms of integer Bessel functions of complex argument. Such solutions, even if commonly not discussed in the literature because diverging at spatial infinity, play a central role in the understanding of the universality of spiral process. In particular,we have studied how in nonlinear reaction-diffusion models the linear part of the equations determines the wave front appearance while nonlinearities are mandatory to cancel out the blowup of solutions. The spiral wave pattern still requires however at least two cross-reacting species to be physically realized. Biological implications of such a results are discussed.

11. A. Pumir, S. Sinha, S. Sridhar, M. Argentina, M. Horning, S. Filippi, C. Cherubini, S. Luther, and V. Krinsky, "Wave-train-induced termination of weakly anchored vortices in excitable media", Phys Rev E vol. 81, 010901 (2010).

    Abstract: A free vortex in excitable media can be displaced and removed by a wave train. However, simple physical arguments suggest that vortices anchored to large inexcitable obstacles cannot be removed similarly. We show that unpinning of vortices attached to obstacles smaller than the core radius of the free vortex is possible through pacing. The wave-train frequency necessary for unpinning increases with the obstacle size and we present a geometric explanation of this dependence. Our model-independent results suggest that decreasing excitability of the medium can facilitate pacing-induced removal of vortices in cardiac tissue.

12. A Gizzi, C Cherubini, S Migliori, R Alloni, R Portuesi and S Filippi, "On the electrical intestine turbulence induced by temperature changes", Phys. Biol. vol.7 016011 (2010)

    Abstract: Paralytic ileus is a temporary syndrome with impairment of peristalsis and no passage of food through the intestine. Although improvements in supportive measures have been achieved, no therapy useful to specifically reduce or eliminate the motility disorder underlying post-operative ileus has been developed yet. In this paper, we draw a plausible, physiologically fine-tuned scenario, which explains a possible cause of paralytic ileus. To this aim we extend the existing 1D intestinal electrophysiological AlievRichardsWikswo ionic model based on a double-layered structure in two and three dimensions. Thermal coupling is introduced here to study the influence of temperature gradients on intestine tissue which is an important external factor during surgery. Numerical simulations present electrical spiral waves similar to those experimentally observed already in the heart, brain and many other excitable tissues. This fact seems to suggest that such peculiar patterns, here electrically and thermally induced, may play an important role in clinically experienced disorders of the intestine, then requiring future experimental analyses in the search for possible implications for medical and physiological practice and bioengineering.